UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,911	07/08/2004	Masakuni Noda	10577.0002-00000	7125

22852 7590 06/30/2008

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
06/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,911	NODA ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6 and 12-37* is/are pending in the application.

4a) Of the above claim(s) *12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 31 March 2008 in response to the Non-Final Office Action mailed 30 October 2007. Claims 12-37 were withdrawn from consideration and claims 1-11 were considered in the 30 October Office Action. Claims 1, 5 and 6 were amended and claims 2-4 and 7-11 were cancelled in the 31 March Paper. Claims 1, 5, 6 and 12-37 are pending and claims 1, 5 and 6 are presently under consideration.

Information Disclosure Statement

In the previous Office Action, Applicant was informed that the IDS filed 1 September 2006 was not considered because it is unsigned. In response, Applicant contends that the IDS was submitted electronically and was signed using an S-signature. Applicant submits as evidence a document purported to be a copy of the IDS that was submitted electronically, which clearly shows the S-signature of Applicant's representative.

Applicant's attention is directed to the IDS image dated 1 September 2006, which can be accessed in PAIR. In contrast to the document submitted with the 31 March Paper as a copy of the 1 September filing, the signature page of the 1 September IDS submission (page 3) is not filled in. In particular, no signature is present on the 1 September submission.

Response to Amendment and Arguments

Claim Objections

Objection to claims 5 as containing informalities is **withdrawn** in view of the amendments thereto.

Claim Rejections - 35 USC § 112/101 "use" claims

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Rejection of claims 1, 5 and 6 under 35 USC § 112 and 101 because the claims provide for the use of a protein but fail to set forth any steps involved in the process is **withdrawn** in view of the amendments to claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 1, 5 and 6 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of the amendment of claim 1 such that the protein of the claims is limited to comprising "the amino acid sequence of SEQ ID NO: 2".

Claims 1, 5 and 6 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is restated below in modified form to account for the claim amendments. Applicant's arguments are addressed following the rejection.

Nature of the invention and Breadth of the claims: The claims are directed to a method of screening for a prophylactic and therapeutic substance for a renal disease comprising determining the level of expression of a protein comprising SEQ ID NO: 2 and determining a binding activity the protein. With regard to scope, it is noted that the claims do not require that the protein comprising SEQ ID NO: 2 is the endogenous gene. Therefore, the claims cover the method wherein expression of the polypeptide is controlled by any regulatory element (e.g., an expression construct comprising a nucleic acid encoding the polypeptide operably linked to a heterologous promoter). In addition, although the claims recite immobilizing a polynucleotide to which the protein is binding to a solid phase, contacting the solid phase with the protein and measuring a binding activity of the protein, the claims do not specify what binding activity is measured. Because the claim does not interrelate the immobilizing and contacting steps with "measuring **a** binding activity" the measured binding activity could be the binding of anything to the protein (e.g., antibodies, small molecules, etc.) in addition to binding of the immobilized polynucleotide implied by the preceding steps. Finally, the claims cover the method practiced in any cell "capable of producing a protein…comprising SEQ ID NO: 2".

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of

a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In the instant case, the claims are directed to using the polypeptide of the claims as a marker for efficacy in the prevention or treatment of any renal disease. In that regard, the art teaches that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (2002) *Dis. Markers* 18:41-46 acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysiologic cascade. Biomarker discovery can also be effected by expression profiling experiment using a variety of array technologies and related methods." However, Wagner cautions, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the

left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44).

Frank *et al.* (2003) *Nature Rev.* 2:566-580 concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng et al. (2004) *Pharmacogenomics* 5:709-719 teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation…A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

Finally, it is noted that the regulation of the expression of any given protein is not uniformly the same in all cell types because different cell types express different regulatory factors. Therefore, one cannot assume that an agent having the capacity to modulate expression of a polypeptide comprising SEQ ID NO: 2 in any given cell type will be capable of modulating expression of the polypeptide in cell types relevant to renal disease.

Viewed as a whole, the art clearly teaches that the utility of a putative biomarker as an indicator of prophylactic and therapeutic efficacy is unpredictable and must be validated.

Amount of direction provided by the inventor and existence of working examples: With regard to renal disease, the application discloses that expression of Egr-1 increased in diabetic

Wistar fatty rats (Example 1), diabetic Zucker fatty rats (Example 2), rat glomerular mesangial cells exposed to serum (Example 3), and spontaneously hypercholesterolemic rats (Example 4). The application also shows that overexpression of Egr-1 protein in a kidney cell line results in expression of fibrosis-related genes (Example 5) and that induced expression of Egr-1 can be inhibited by an angiotensin II receptor antagonist in the Zucker fatty rat (Example 2) and rat mesangial cells (Example 3) and by an Egr-1 antisense oligonucleotide in cultured mesangial cells (second "Example 1" beginning on page 74).

The application asserts, "The present inventors… have for the first time found out that the expression of renal Egr-1 in a renal disease model animal is remarkably increased, and further for the first time that suppression of the expression of renal Egr-1 in a renal disease model animal can produce a therapeutic effect on a renal disease. The present inventors have further carried out studies based on findings thereof, thus leading to the completion of the present invention." However, the application appears to contain only data showing altered expression of Egr-1 in certain disease models, which the art does not recognize as sufficient to establish that the protein is a valid surrogate endpoint for identifying therapeutic and prophylactic agents. Contrary to Applicant's assertion, there does not appear to be any evidence presented demonstrating that an agent that alters the expression or function of Egr-1 produces a therapeutic effect in a disease model. In addition, no evidence at all is presented evidencing that a substance capable of inhibiting expression and/or a binding activity of a protein comprising SEQ ID NO: 2 could be used to prevent a renal disease as recited in the claims.

It is further noted that because Egr-1 RNA was measured in the examples, which is most likely regulated at the level of expression from the endogenous gene, there is no evidence that

expression of a protein comprising SEQ ID NO: 2 can be used as a marker for an agent capable of preventing or treating renal disease independent of the endogenous Egr-1 gene regulatory elements. In addition, the application does not contemplate any binding activities that might be used to identify an agent having the recited properties other than binding to a polynucleotide to which the protein is capable of binding. (See especially the second paragraph on page 31.)

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to use the claimed invention to identify a prophylactic and therapeutic substance for diseases associated with the protein of the claims without first having to engage in undue experimentation to establish that the expression or binding of the protein is a valid marker for renal disease and response to a substance capable of preventing and treating that disease. The art clearly establishes that putative biomarkers must be validated and that "few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation" (Feng *et al.*, *Id.*).

Given this high degree of unpredictability and the absence of evidence demonstrating that expression or function of the protein of the claims is a valid surrogate endpoint for therapeutic efficacy in any disease associated with the protein, the basic premise underlying the claimed invention is no more than a theoretical possibility. This is not sufficient to meet the enablement requirement of 35 USC §112, first paragraph.

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor,

> or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. *Genentech Inc. v. Novo* Nordisk A/S (CA FC) 42 USPQ2d 1001, 1005.

Furthermore, even if the invention were enabled for identifying a prophylactic or therapeutic substance for a renal disease by measuring expression of an endogenous gene encoding SEQ ID NO: 2 in a specific cell type (e.g., glomerular mesangial cells) and/or binding of a polypeptide comprising SEQ ID NO: 2 to DNA, extending the teachings of the specification such that the method could be practiced as broadly as claimed would require undue experimentation.

In view of the foregoing, it would require undue experimentation to practice the invention claimed. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

Response to Arguments

In response to the *prima facie* rejection of record, Applicant submits that the claims are not drawn to any polypeptide and any disease. Instead, the claims require a protein or salt thereof "comprising the amino acid sequence of SEQ ID NO: 2." In addition, the claims require that the disease is a renal disease.

While this is acknowledged, it is also true that the amended claims cover identifying an agent capable of preventing or treating a renal disease the method wherein expression of the polypeptide is controlled by any regulatory element (e.g., an expression construct comprising a nucleic acid encoding the polypeptide operably linked to a heterologous promoter) in any cell capable of producing said protein. In addition, because the claim does not interrelate the

immobilizing and contacting steps with "measuring **a** binding activity" the measured binding activity could be the binding of anything to the protein (e.g., antibodies, small molecules, etc.) in addition to binding of the immobilized polynucleotide implied by the preceding steps. As the application disclosure does not extend beyond expression of mRNA from the endogenous Egr-1 gene in kidney cells and prophetic statements limited to binding of Egr-1 protein to nucleic acids, the claim scope is still broad.

In response to the Examiner's contention that there does not appear to be any evidence presented demonstrating that an agent that alters the expression or functions of Egr-1 produces a therapeutic effect in a disease model Applicant submits that the instant claims are drawn to a method of screening, as opposed to a method of treatment.

While it is acknowledged that the claims are directed to a method of screening, the claims explicitly recite the intended use of "screening for a prophylactic and therapeutic substance for renal disease" and when a claim is limited to a specific use enablement is determined based on the recited use. (See MPEP 2164.01(c).)

Applicant additionally submits that working examples are not required and cites MPEP 2164.02 as stating "[c]ompliance with the enablement requirement or 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed" and that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement.". Moreover, Applicant contends, an "applicant need not have actually reduced the invention to practice prior to filing." Id. Applicant cites the Federal Circuit in *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 U.S.P.Q. 2d 1302, 1304 (Fed. Cis. 1987) as holding that "[t]he mere fact that something has not previously been done

clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

This argument has been fully considered but is not deemed persuasive. First, it is respectfully noted that the conclusion that the claims are not enabled is not "the sole reason for rejection the claimed invention on the grounds of lack of enablement" as implied by Applicant's remarks. Instead, the rejection is based on a complete analysis of the claim scope, the state of the relevant art, the disclosure of the instant application and the relevant law. (See *supra*.) As stated in MPEP 2164.02 (emphasis added):

> "The specification need not contain an example **if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation**. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).
>
> Lack of a working example, however, is a factor to be considered, **especially in a case involving an unpredictable and undeveloped art**.

The *prima facie* rejection establishes that the relevant art is highly unpredictable. Therefore, the absence of a working example is a relevant factor to be considered in determining whether the claims are enabled. In addition, the courts have found that, in an unpredictable art, an untested hypothesis is not sufficient basis for a patentable invention. See *Genentech Inc. v. Novo* Nordisk A/S (CA FC) 42 USPQ2d 1001, 1005:

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

See also, *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297 (Fed. Cir. 2005) wherein in response to Rasmusson's argument that the enablement requirement of section 112 does not mandate a showing of utility or, if it does, it mandates only a showing that it is "not implausible" that the invention will work for its intended purpose, the Court states, "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Finally, Applicant submits that the specification does provide a clear link between Egr-1 and renal disease and cites Examples 1 and 5 of the specification.

In response, the disclosed examples were acknowledged in making the *prima facie* rejection (see *supra*). However, the rejection also cites Wagner as teaching, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" and "Biomarkers require validation in most circumstances"; Frank et al. as teaching, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action"; and Feng et al. as teaching, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the

biomarkers showing promise in initial discovery were found to warrant subsequent validation…A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract). In view of the record as a whole, one would not conclude that a link between Egr-1 and renal disease does not establish expression of Egr-1 and/or binding of Egr-1 to DNA as a valid surrogate endpoint for prophylactic or therapeutic efficacy in the treatment of renal disease.

Thus, in view of the record as a whole, one must conclude that the showings of the application do not sufficiently establish expression and binding of a polypeptide comprising SEQ ID NO:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of claims 1, 5 and 6 under 35 U.S.C. 102(b) as being anticipated by any one of Rosenberg (1993) *Kidney Int.* 43:601-609, Rupprecht et al. (1993) *Am. J. Physiol.* 265:F351-F360, or Kim et al. (1995) *Circulation* 92:88-95, Hofer et al. (1996) *J. Biol. Chem.* 271:28306-28310, Rupprecht et al. (1997) *Kidney Int.* 51:694-702, Khachigian et al. WO 97/32979, Einstein et al. WO 01/04356 A1, Alberini et al. WO 01/74298 A2, or Rupprecht et al. (2000) *Kidney Int.* 57:70-82 is **withdrawn** in view of the amendment of claim 1 to require a combination of process steps not disclosed in the prior art references.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rupprecht et al. (2000) *Kidney Int.* 57:70-82 (hereinafter, Rupprecht '00; previously made of record) in view of McKay et al. (1998) *Anal. Biochem.* 265:28-34 and further in view of Raugi et al. (1987) *Am. J. Pathol.* 129: 364-372.

Claim 1 is directed to a method comprising (a) cultivating a cell capable of producing a protein comprising the amino acid sequence of SEQ ID NO:2 in the absence and presence of a test compound; (b) measuring production of the protein; (c) comparing production of the protein when the cell is cultivated in the absence of a test compound and the production of the protein

when the cell is cultivated in the presence of a test compound; (d) immobilizing on a solid phase a polynucleotide to which the protein is capable of binding; (e) contacting the solid phase with the and an antibody against the protein; (f) measuring a binding activity of the protein; (g) comparing the binding activity of the protein when the cell is cultivated in the absence of the test compound and when the cell is cultivated in the presence of the test compound; and (h) selecting a compound that (1) decreases the production of the protein or salt thereof and/or (2) decreases the binding activity of the protein or salt thereof.

Rupprecht '00 teaches a method comprising comparing the expression of an Egr-1 protein in rat glomerular mesangial cells in the absence (i.e., serum only) and presence of a test compound (i.e., GSNO or 8Br-cGMP). (See especially Figures 5 and 6 and the captions thereto.) Furthermore, Rupprecht '00 teaches a method comprising comparing expression of a reporter gene under the transcriptional control of Egr-1 in the absence and presence of a test compound. (See especially Figure 9 and the caption thereto.) Still further, Rupprecht '00 teaches a method comprising comparing binding of Egr-1 to a polynucleotide comprising the Egr-1 binding site wherein the method uses the polynucleotide and an antibody against Egr-1 (i.e., supershifting). (See especially Figures 7 and 8 and the captions thereto.) Finally, Rupprecht '00 teaches that GSNO inhibits the expression and DNA binding activity of Egr-1 to DNA. (See especially Figures 5 and 7 and the captions thereto.) The method of Rupprecht '00 is the same as the method claimed in the instant application except that Rupprecht '00 does not teach the steps of immobilizing a polynucleotide on a solid support and contacting the solid phase with the protein and an antibody against the protein. In addition, Rupprecht '00 teaches the method using rat cells and therefore the polypeptide comprises the sequence of the rat Egr-1 ortholog.

McKay et al. teaches that ELISA assays for determining the DNA binding activity of DNA binding proteins involving immobilization of a target DNA to a solid support and contacting the solid support with the DNA binding protein and an antibody that binds to the DNA binding protein were known in the art. (See especially the abstract, the section entitled "ELISA" beginning at the bottom of page 31, Figure 3 and the caption thereto.) In addition, McKay et al. teaches that the ELISA assay described therein is an art recognized alternative to the EMSA assay used in the method of Rupprecht '00. (See especially the abstract.) Furthermore, the teachings of Raugi et al. demonstrate that cultured human glomerular mesangial cells, which inherently express the Egr-1 polypeptide comprising SEQ ID NO: 2, were available in the art and used in methods of characterizing mesangial cell function at the time the instant invention was made. (See throughout.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Rupprecht '00 by substituting the ELISA assay of McKay et al. for the EMSA assay used in the method of Rupprecht '00 and the human glomerular mesangial cells of Ragui et al. for the rat glomerular mesangial cells of Rupprecht '00.
In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At 1395.)

In the instant case, the method of Rupprecht '00 comprises all of the elements of the invention presently claimed except for the substitution of an EMSA assay for the ELISA assay of the claims and the substitution of a polypeptide comprising the rat ortholog of Egr-1 for the human Egr-1 polypeptide comprising SEQ ID NO: 2 of the claims. However, the teachings of McKay et al. and Ragui et al. demonstrate that ELISA-based assays of measuring protein binding to DNA and cultured human glomerular mesangial cells were known in the art at the time the invention was made. Furthermore, the teachings of the secondary references demonstrate that the ELISA assay was recognized as an alternative to EMSA for determining the effects of agents on protein binding and cultured human mesangial could be used in methods of determining mesangial cell function. Thus, all of the elements of the method and there uses were known to one of ordinary skill in the art at the time the invention was made and the skilled artisan could have substituted one known element for another element known in the art to obtain the predictable outcome of an assay for determining the effects of an agent on human Egr-1 expression and binding to DNA. With regard to the intended uses recited in the claims, the application does not point out any unique steps that are implied by the recited intended use other than a determination that expression of the protein or binding of the protein to DNA is decreased. As the method of Rupprecht et al. '00 in view of McKay et al. and further in view of Raugi et al. comprises all of the elements of the invention presently claimed and Rupprecht '00 teaches identifying a compound that inhibits both expression and DNA binding activity of Egr-1 the intended use is not considered to distinguish the method presently claimed from the prior art method.

In view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636